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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/682,230	10/09/2003	Jonathan Robert Lamb	674525-2006	7496

20999 7590 12/19/2008
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EXAMINER
HOWARD, ZACHARY C

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
12/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/682,230	LAMB ET AL.
	Examiner	**Art Unit**
	ZACHARY C. HOWARD	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 20 October 2008.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,2,4-10,12-16,25 and 26 is/are pending in the application.

4a) Of the above claim(s) 5,7,8,13,15,16,25 and 26 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,4,6,9,10,12 and 14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1,2,4-10,12-16,25 and 26 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 04 March 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 10/20/08 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 10/20/08 has been entered in full. Claims 17-24 are canceled. (Claims 3 and 11 were previously canceled).

Claims 25 and 26 are listed with the status of "(Previously presented)". However, the correct status of these claims should be "(New)" because they were previously presented in the "not fully responsive" response filed on 5/28/08 (see page 2 of the Miscellaneous Action mailed on 8/18/08). Claims 25 and 26 are herewith entered as "New" claims. However, these new claims do not read upon the elected species of "upregulator". The instant specification does not contemplate "antibodies" as "upregulators" of the Hedgehog signaling pathway. The specification teaches only that antibodies may be antagonists of the Hedgehog signaling pathway (¶ 70 of the published application). Therefore, claims 25 and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 5, 7, 8, 13, 15 and 16 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are under consideration, in so far as they read on the elected species of (1) “Sonic Hedgehog signaling pathway” and (2) “upregulator”.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of upregulating T-cell activation, or proliferation, comprising administering to *in vitro* T-cells an anti-CD3 antibody, anti-CD28 antibody and the 19kDa N-terminal autoproteolytic Sonic hedgehog (Shh) peptide, does not reasonably provide enablement for a method of modulating T-cell activation or proliferation comprising administering to T-cells a modulator of a Hedgehog signaling pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was set forth previously and maintained at pg 3-6 of the 11/28/07 Office Action.

Applicants' arguments (9/10/07; pg 5-7) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants first argue that the skilled artisan can practice the claimed invention "in an *in vitro* treatment setting without undue experimentation". Applicants argue that a working example is not required for enablement (pointing to MPEP 2164.02). Applicants argue that "the guidance provided in the specification for *in vitro* application of the present invention sufficiently enables one skilled in the art to use the Shh protein as a modulator of T-cell activation *in vitro*". Applicants argue that this guidance includes a description of the Shh protein (page 16, line 12 to page 17, line 8) and methods for isolating T-cells (page 91, Example 3).

Applicants' arguments have been fully considered but are not found to be persuasive. It is acknowledged that a working example is not necessarily required for enablement. However, it is maintained that instant specification does not provide any guidance on how to use the Shh protein as an *in vitro* modulator of T-cell activation in the absence of anti-CD3 and anti-CD28 antibodies, and it would require undue experimentation to determine how to use the Shh protein in this manner. Example 13 of the specification provides evidence that the claimed method will not work *in vitro* in the absence of anti-CD3 and anti-CD28 antibodies. Example 13, lines 14-15 state "No significant difference in the degree of proliferation was observed following the addition of the Shh peptide in resting CD4+ T-cells" (pg 96). The description of the Shh protein and methods of isolating T-cells in the reference pages of the specification do not provide teachings that compensate for the absence of anti-CD3 and anti-CD28 antibodies in the claimed method as practiced *in vitro*. The skilled artisan would need to engage in undue experimentation to screen a vast genus of potential test compounds for other potential activators (which may not even exist) prior to using the claimed method *in vitro* without the anti-CD3 and anti-CD28 antibodies.

Applicants further argue that an "extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance" (quoting *In re Colianni* (1997)). Applicants argue that the “specification provides numerous examples of various upregulators that are encompassed by the claimed invention” (pointing to page 18, line 28 to page 22, line 18) and “assays that can be used to confirm activity of any particular upregulator" (pointing to page 22, line 19 to page 23, line 17).

Applicants' arguments have been fully considered but are not found persuasive. The specification from page 18, line 28 to page 22, line 18 includes the general statement that “compounds that increase (agonise) Hedgehog signaling” (pg 19, lines 5-6) but provides extremely limited (as compared to the breadth of the genus of potential upregulators) guidance regarding specific upregulators that can be used in the claimed method. In this section, the only specific upregulators that are disclosed are “[e]xamples of such agonists include the positive regulators of HH signaling Smo and Gli” (pg 20, lines 24-25). However, as set forth previously, the structure and functionality of these compounds differ significantly from Shh; specifically, while Shh is a secreted ligand of a cell-membrane receptor (Patched), Smo receptor is a membrane-bound receptor and Gli is a cytoplasmic protein. The skilled artisan would predict that these compounds would not activate the Hedgehog signaling pathway in the cell-based assay described on page 23 of the specification. There is no working example of a method wherein T-cells are contacted with either the Smo receptor or the Gli protein that results in T-cell activation or proliferation, and it would require undue experimentation to determine how a membrane-bound or intracellular protein could be administered to function as an upregulator of the Hedgehog signaling pathway.

In order the practice the claimed method of modulation with a genus of “upregulators”, the skilled artisan must identify said upregulators without undue experimentation. The disclosure of an assay to screen a vast genus of potential upregulators of the signaling pathway does not allow the skilled artisan to identify upregulators that will function in the claimed method. As set forth previously, the claims encompass methods of upregulating T-cell activation, or proliferation, with upregulators of a Sonic Hedgehog (Shh) signaling pathway other than the biologically active 19kDa N-terminal autoproteolytic Shh peptide. The claims encompass a vast genus of potential upregulators including compounds such as small molecules, proteins, nucleic acids, and more. However, the specification provides little guidance as to the nature of specific upregulators of Shh signaling pathway that can be used able to modulate T-cell activation or proliferation. The specification provides a single working example of an upregulator (19kDa N-terminal autoproteolytic Shh peptide) that works in the claimed method when practiced *in vitro*. The specification further teaches that a large variety of small molecules that are “modulators” of the hedgehog signaling pathway (pages 38-51). However, there is no guidance provided by the specification as to which of these small molecules are upregulators and which are inhibitors. There is no guidance regarding the mechanism of interaction of these molecules with a Hedgehog pathway. Furthermore, there is no working example of a method wherein one of these putative Hedgehog signaling modulators is used specifically for T-cell activation or proliferation. The specification merely demonstrates that T-cells can be contacted with the Shh peptide to activate the T-cells, and then suggests that any agonist of a Shh signaling pathway can be used in a similar manner. In view of the breadth of the genus of upregulators encompassed by the claims and the minimal guidance regarding specific upregulators in said genus that will work to activate or proliferate T-cells, the claims lack enablement for the full scope of the claims. The specification merely invites the skilled artisan to screen a large genus of potential compounds to identify upregulators of a Shh signaling pathway that can possibly upregulate T-cell activation or proliferation.

Applicants further argue that, “the specification provides substantial guidance for practicing the present invention *in vivo*” (pg 6). Applicants argue that the specification describes the form, route and dosage for administration of a modulator and point to teachings on pages 80 and 83. Applicants further argue that "the examples of applying modulators to isolated T-cells from specification [sic], most notably Example 13, correlates to the instant claims, which encompasses in vivo methods of treatment". Applicants argue that the Examiner admitted in the previous Office Action that Example 13 demonstrates a correlation to an in vivo setting by admitting that the administration of anti-CD3 or anti-CD28 antibodies mimics an ongoing immune response.

Applicants' arguments have been fully considered but are not found persuasive. The teachings on pages 80 and 83 of the specification provide lists of potential routes of administration and dosages of modulators. However, as set forth in the previous Office Action, the specification does not provide any working examples of modulation of *in vivo* T-cell activation or proliferation with modulators. Furthermore, it is maintained that the relevant art supports that the skilled artisan could not predict whether or not administration of Shh or a modulator of a Shh signaling pathway would result in an increase, a decrease or no effect on T-cell activation or proliferation. Outram et al (2000) teaches that Shh inhibits thymocyte development in the DN (double negative) CD4- CD8- stage (Outram et al, 2000. Immunity. 13: 187-197; cited previously). Thus, Sonic hedgehog signaling is involved in other *in vivo* processes related to thymocytes that may interfere with T-cell activation or proliferation (i.e., inhibition of development is contradictory to activation). The previous Office Action did not indicate that "Example 13 demonstrates a correlation to an in vivo setting by admitting that the administration of anti-CD3 or anti-CD28 antibodies mimics an ongoing immune response". Instead, the Office Action stated that (to quote) "T-cell activation via the cell-surface molecules CD3 and CD28 are part of an ongoing immune response and that the response of cells to antigens does not require administration of anti-CD3 or anti-CD28 antibodies" (pg 3 of the 11/28/07 Office Action). This statement was solely directed to T-cell activation *in vivo* and was not a commentary on Example 13. Instead, the teachings of Outram provide evidence that the simplified *in vitro* model used in Example 13 does not correlate with the complexity of the claimed invention as practiced *in vivo*. In view of this unpredictability, the skilled artisan would need to engage in undue experimentation to determine whether or not Shh, or another modulator of a Shh signaling pathway or another target pathway, could be used for any form of *in vivo* modulation (such as treatment). This undue experimentation would need to be completed prior to any routine determination of optimal methods of administration or dosages.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth previously and maintained at pg 6-8 of the 11/28/07 Office Action.

Applicants’ arguments (9/10/07; pg 7-8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the presence of working examples demonstrating use of Smo receptor or the Gil [sic] protein is not necessary so long as the Applicants demonstrate possession of the claimed invention at the time of the filing date" (pg 7). Applicants point to pg 15, line 19 to page 16, line 20 as having a "substantial description of the Smo receptor or the Gil [sic] protein" and Example 13 as having a demonstration of using modulators to affect T-cell activation and proliferation.

Applicants' arguments have been fully considered but are not found persuasive. Pages 15 and 16 of the specification merely describe the Hedgehog signaling pathway, including Smoothened (Smo) and Gli. Example 13 is directed solely to the use of the Shh peptide. There is no description of the use of Smo or Gli as a modulator of T-cell activation and proliferation. As set forth previously, Smo and Gli are significantly different than Shh in function; specifically, while Shh is a secreted protein that acts on a cell surface receptor (Patched), the Smo receptor is membrane-bound and Gli is an intracellular protein. Based on these significant structural and functional differences, the skilled artisan would predict that these compounds would not activate the Hedgehog signaling pathway in the cell-based assay described on page 23 of the specification. There is no description of a method wherein T-cells are contacted with the Smo receptor or the Gli protein that results in T-cell activation or proliferation. As such, the skilled artisan would not consider these compounds to represent described compounds that could be used in the claimed method as upregulators.

Applicants further argue that "it would be clear to a skilled artisan which modulators can be used as upregulators of the present invention" (pg 8). Applicants argue that specification describes the Hedgehog signaling pathway (page 15, line 12 to page 18, line 7) and a representative number of species of upregulators of a Hedgehog signaling pathway (page 18, line 28 to page 22, line 18). Applicants further argue "that a large number of modulators that can upregulate Shh signaling are known in the art, including the protein and non-protein organic molecules described in the specification".

These arguments have been fully considered but are not found persuasive. The specification from page 18, line 28 to page 22, line 18 includes a general statement regarding “compounds that increase (agonise) Hedgehog signaling” (pg 19, lines 5-6) but provides extremely limited (as compared to the breadth of the genus of potential upregulators) description of the structure of specific upregulators. In this section, the only specific upregulators that are disclosed are “[e]xamples of such agonists include the positive regulators of HH signaling Smo and Gli” (pg 20, lines 24-25). However, as described above, the skilled artisan would not consider these compounds to represent described compounds that could be used in the claimed method as upregulators. Furthermore, the genus of potential upregulators is highly variant because an essentially unlimited number of structural differences are permitted between genus members. Potential genus members include chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. At the time of filing of the instant application (April 9th, 2002), the relevant art did not appreciate upregulators of Shh signaling that were commensurate in scope with the breadth of the “upregulator” genus encompassed by the claims. The specification describes the Sonic hedgehog protein as an upregulator of the pathway that can be used in the claimed invention. Pages 38-51 provide a large variety of small molecules that are described as “modulators” of the hedgehog signaling pathway. However, there is no description of which of these small molecules are upregulators and which are inhibitors. There is no description of the mechanism of interaction of these molecules with the hedgehog pathway. Most importantly, there is no description of a method wherein one of these molecules is used for T-cell activation or proliferation. Therefore, for the reasons set forth in the previous Office Action, it is maintained that only a method of modulating T-cell activation or proliferation comprising contacting T-cells with the 19kDa N-terminal autoproteolytic Sonic hedgehog peptide, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Gool et al, 1993 (The Journal of Immunology. 150(8): 3254-3263; cited previously). This rejection was set forth previously and maintained at pg 9 of the 11/28/07 Office Action.

Applicants’ arguments (9/10/07; pg 8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that "[i]n the case of Van Gool et al, the modulator, i.e., the anti-CD3 and anti-CD28 antibodies, are not being "applied" or "given" to T-cells, but rather the T-cells are being placed on into [sic] culture plates coated with the anti-CD3 and anti-CD28 antibodies" (pg 8).

Applicants' arguments have been fully considered but are not found persuasive. The claims recite "administering to T-cells a modulator of a Hedgehog signalling pathway". In the original rejection set forth on page 13 of the 3/9/07 Office Action, the anti-CD3 and the anti-CD28 antibodies were not held to be modulators of a Hedgehog signaling pathway. Rather, it was stated that (to quote) "any prior art method of contacting T-cells with sub-optimal does of anti-CD3 and anti-CD28 antibody would inherently result in "contacting T-cells with a modulator of a Hedgehog signaling pathway" because T-cells would secrete and come into contact with the Shh protein". Thus, the instant rejection is based on the Shh protein being considered to be the modulator of a Hedgehog signaling pathway as recited in the claims. Applicants have subsequently amended the claim to change the word "contacting with" to "administering to", and argue that "administration" requires some sort of action (not specified) by the skilled practitioner that is different than contacting. However, the instant specification does not provide a limiting definition of the term “administering”. As set forth previously, the definition of the term “administer” includes “to make application; give” (see the first page of the Dictionary.com definition of “administer”; cited previously). Culturing T-cells on plates coated with anti-CD3 and anti-CD28 antibodies would inherently cause the cells to secrete Shh, which would then come into contact with the cells. This teaching meets the definition of administer with respect “to make application”; i.e., the methodology taught by Van Gool results in Shh being "applied" to the T-cells. As the term “administering” encompasses *in vitro* application of modulators to T-cells, it is maintained that the teachings of Van Gool anticipate the claims for the reasons set forth previously.

Applicants further argue that "[t]he specification provides examples of "administration" of the modulators of the invention (page 83, line 4 – page 86, line 29) which are clearly different than the methods of Van Gool et al" (pg 8).

Applicants' arguments have been fully considered but are not found persuasive. It is acknowledged that the teachings regarding administration found at the specified pages of the specification differ from the methods of Van Gool et al; however, these differences are not reflected in the instant claims. Pages 83, line 4 to page 86, line 29 of the specification are directed to "administration" for therapy; i.e., *in vivo* methods of administration. However, the instant claims are not limited to methods comprising administration of a modulator to a subject. Instead, the claims encompass *in vitro* methods where compounds are administered to cells, such as taught by Van Gool et al.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Outram et al, 2000 (Immunity. 13:187-197; cited previously). This rejection was set forth previously and maintained at pg 10-11 of the 11/28/07 Office Action.

Applicants' arguments (5/28/08; pg 8-9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants argue that the teachings of Outram et al are "related to thymocyte development" and not to modulating T-cell activation or proliferation as recited in the instant claims. Applicants argue that the "cited references must teach a method of modulating T-cell activation or modulating T-cell proliferation in order to be considered anticipatory prior art". Applicants argue that the claim preamble must be read in the context of the entire claim and point to MPEP 2111.02. Applicants further point *In re Jansen v. Rexall Sundown, Inc* (2003), which is cited in MPEP 2111.02.

Applicants' arguments have been fully considered but are not found persuasive. The preamble of the instant claim has been read in context of the entire claim. MPEP 2111.02 further states, "[i]f the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction". In the instant case, the body of the claimed method sets forth all of the limitations of the claimed method. For example, in independent claims 1 and 9, the body of the claim sets forth the limitation of "administering to T-cells a modulator of Hedgehog signalling pathway". The preamble of claim 1 or 9 merely states the intended use of said administration rather than any distinct definition of any of the claimed invention's limitations. Therefore, as set forth previously, the recitation of “modulating T-cell activation” or “modulating T-cell proliferation” in the preamble of the claims from the instant application is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Furthermore, the specification provides no limiting definition of “T-cell activation” or “T-cell proliferation”. Therefore, the claims have been interpreted as encompassing any method of “activating” a cellular process in T-cells comprising contacting T-cells with a modulator of Hedgehog signaling.

With respect to *In re Jansen v. Rexall Sundown, Inc* (2003), which is cited in MPEP 2111.02, the fact patterns of the case and of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections. Specifically, discussing *In re Jansen*, MPEP 2111.02 states that "the court held that the claims’ recitation of a patient or a human “in need” gives life and meaning to the preamble’s statement of purpose". Thus, this decision relates to claims wherein the preamble specifies a particular patient population (those "in need") that is narrower than the general patient population (including those "in need" and those that are not). This differs significantly from the instant claims which do not specify modulation of a particular T-cell population that narrows the population recited in the body of the claim.

As set forth previously, Outram teaches that a “neutralizing antibody against Shh accelerates thymocyte development in thymus explants” (pg 188). Outram teaches “culturing thymocytes with the anti-Hh neutralizing antibody 5E1” and “neutralization of Shh greatly increased thymocyte differentiation over this 3 day time period” and “there was a 2- to 3.5- fold increase in the number of thymocytes recovered from the cultures containing the neutralizing antibody” (pg 188-189). Therefore, Outram teaches a method of comprising contacting T-cells with a modulator of Hedgehog signaling and anticipates instant claims 1, 2, 4, 9, 10 and 12. Claims 6 and 14 each encompass a modulator that is an “antibody”. Therefore, the method taught by Outram comprising contacting T-cells with anti-Shh antibody also anticipates each of claims 6 and 14.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al, December 2000 (Immunology. 101(Supplement 1): pg 14; cited previously). The publication date of Stewart (12/00) is more than one year prior to the earliest U.S. filing date to which the instant application claims priority (4/9/02). This rejection was set forth previously and maintained at pg 11 of the 11/28/07 Office Action.

Applicants’ arguments (5/28/08; pg 9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that "Steward [sic] et al., while merely relating to T-cell proliferation, does not teach this limitation" (pg 9).

Applicants’ arguments have been fully considered but are not found persuasive. Stewart specifically states that "[t]he addition of Shh enhances the proliferative response of both CD4+ and CD8+ cells following stimulation with αCD3 and αCD28". Therefore, Stewart not only relates to "T-cell proliferation", Stewart explicitly teaches that T-cell proliferation is enhanced (which is a form of modulation) by Shh (Sonic hedgehog). Claim 9 specifically recites “[a] method of modulating T-cell proliferation”. Therefore, Applicants’ arguments are not persuasive in this regard because claims 9, 10, 12 and 14 each encompass T-cell proliferation, which is explicitly is taught by Stewart. Furthermore, as set forth previously, the teachings of Stewart are also directed to T-cell activation. Specifically, stimulation with anti-CD3 and anti-CD28 antibodies inherently causes T-cell activation. Therefore, Applicants’ arguments are also not persuasive with respect to claims 1, 2, 4 and 6. It is maintained that Stewart anticipates the instant claims for the reasons set forth previously.

Applicants further argue that "Stewart et al. only recites that the addition of Shh enhances the proliferative response, and the cited reference does not provide enough information to be consider [sic] as an enabling disclosure". Applicants argue that a "reference contains an enabling disclosure if the person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. Applicants point to *In re Donohue* (1985) in support.

Applicants’ arguments have been fully considered but are not found persuasive. Applicants' characterization of what constitutes an enabling disclosure as held in the decision *In re Donohue* (1985) is not disputed. However, Applicants have not provided any evidence that Stewart et al does not enable the skilled artisan to practice an invention encompassed by the instant claims. Stewart et al teaches that "[t]he addition of Shh enhances the proliferative response of both CD4+ and CD8+ cells following stimulation with αCD3 and αCD28". Recombinant Sonic hedgehog protein, CD4+ T cells, CD8+ cells, anti-CD3 antibodies (αCD3) and anti-CD28 antibodies (αCD28) were all well known in the art prior to the publication of Stewart et al. Stewart merely discloses that a method of adding Shh to T cells increases proliferation following stimulation with said antibodies. This method is fully encompassed by the instant claims for the reasons set forth previously and maintained herein. Applicants fail to specify what exactly is non-enabling regarding the teachings of Stewart et al, i.e., why the skilled artisan, when practicing the method described by Stewart et al, would fail to observe the enhanced proliferation described therein. Furthermore, Applicants' own working examples in the specification provide evidence that Shh enhances the proliferative response of both CD4+ and CD8+ cells following stimulation with αCD3 and αCD28. Finally, it is noted that two Applicants (Jonathan Lamb and Gerald Hoyne) are included as authors of the Stewart publication and the publication appears to describe Applicants' own work that is also described in the instant specification.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE**

FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646
/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646